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CERTIFICATION UNDER 37 CFR 1.10

I hereby certify that this New Application Transmittal and the documents referred to as enclosed therein are being deposited with the United States Postal Service on this date April 10, 2000 in an envelope as "Express Mail Post Office to Addressee" Mailing Label Number EL 261867320US addressed to the: Director of the United States Patent and Trademark Office., Washington, D.C. 20231.

Pamela Johnston

(Print Name)

Pamela Johnston

(Signature)

1c554 U.S. PTO

09/546143

04/10/00

Director of the United States Patent and Trademark Office
BOX PATENT APPLICATION
Washington, D.C. 20231

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, NJ 07110
Case Docket 9473
April 10, 2000

Sir:

Transmitted herewith for filing under 37 C.F.R. § 1.53(b) is the patent application of

Inventor(s): Peter Karl Matzinger, Michelangelo Scalone, Ulrich Zutter.

For: ASSYMETRIC SYNTHESIS PROCESS

Enclosed are:

1. _____ sheet(s) of drawing. [] formal [] informal
2. X 3 page(s) of Declaration and Power of Attorney
3. _____ page(s) of Sequence Listing
4. _____ computer disk(s) containing Sequence Listing
5. _____ Statement under 37 CFR § 1.821 or 37 C.F.R. § 1.825
6. X 24 pgs. of specification, 11 pgs. of claims, 1 pg. of abstract, Preliminary Amendment

DEPOSIT ACCOUNT

NO. 08-2525

OUR ORDER NO. 3104..

7. The fee has been calculated as shown below:

CLAIMS				
FOR	NO. FILED	NO. EXTRA	RATE	FEE
TOTAL CLAIMS	18 - 20	0	x \$18	0
INDEP. CLAIMS	10 - 3	7	x \$78	546.00
MULTIPLE DEPENDENT CLAIMS PRESENTED			+ \$260	
BASIC FEE				\$690.00
TOTAL				<u>\$ 1236.00</u>

8. X Please charge my Deposit Account No. 08-2525 in the amount of \$ 1236.00. This sheet is provided in triplicate.

9. A check in the amount of \$ to cover the filing fee is enclosed.

10. X The Commissioner is hereby authorized to charge payment of the following fees or any additional fees associated with this communication or credit any overpayment to Deposit Account No. 08-2525. This sheet is provided in triplicate.

 X Any filing fees required under 37 C.F.R. § 1.16.

 X Any patent application processing fees under 37 C.F.R. § 1.17.

11. Priority - 35 U.S.C. § 119

FOREIGN PRIORITY

[X] Foreign Priority of application(s) number 96105998.7 filed on April 17, 1996 in Europe is claimed under 35 U.S.C. § 119(a)-(d) or 35 U.S.C. § 365(a)-(b).

[X] The certified copy(ies) has(have) been filed in prior U.S. patent application Serial No. 08/832,253 on November 3, 1997.

[] The certified copy(ies) will follow.

12. RELATION BACK UNDER 35 U.S.C. § 120

(A) ☒ Amend the specification by inserting, before the first line, the following sentence: -- This is a ☐ continuation ☒ divisional of copending application(s) ☐ Serial No. 09/195,512 filed on November 19, 1998, which is a continuation of Serial No. 08/832,253 filed April 3, 1997. --

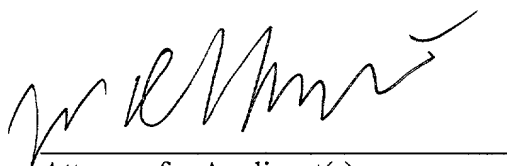
(B) ☒ A copy of the oath or declaration from the prior application noted above is enclosed.

13. ☒ The power of attorney in prior application is to:

George W. Johnston (Reg. No. 28090), William H. Epstein (Reg. No. 20008), Dennis P. Tramaloni (Reg. No. 28542) and Patricia S. Rocha-Tramaloni (Reg. No. 31054), Ellen C. Coletti (Reg. No. 34140), Raina Semionow (Reg. No. 39022), Catherine Roseman Smith (Reg. No. 34240).

- a. ☐ The power appears in the original papers of the prior application.
- b. ☐ Since the power does not appear in the original papers, a copy of the power in the prior application is enclosed.
- c. ☒ Recognize as associate attorney Lewis J. Kreisler (Reg. No. 38522).
- d. Continue to address all communications to

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96994

1. 1990-1991 2. 1991-1992 3. 1992-1993 4. 1993-1994 5. 1994-1995 6. 1995-1996 7. 1996-1997 8. 1997-1998 9. 1998-1999 10. 1999-2000 11. 2000-2001 12. 2001-2002 13. 2002-2003 14. 2003-2004 15. 2004-2005 16. 2005-2006 17. 2006-2007 18. 2007-2008 19. 2008-2009 20. 2009-2010 21. 2010-2011 22. 2011-2012 23. 2012-2013 24. 2013-2014 25. 2014-2015 26. 2015-2016 27. 2016-2017 28. 2017-2018 29. 2018-2019 30. 2019-2020 31. 2020-2021 32. 2021-2022 33. 2022-2023 34. 2023-2024 35. 2024-2025 36. 2025-2026 37. 2026-2027 38. 2027-2028 39. 2028-2029 40. 2029-2030 41. 2030-2031 42. 2031-2032 43. 2032-2033 44. 2033-2034 45. 2034-2035 46. 2035-2036 47. 2036-2037 48. 2037-2038 49. 2038-2039 50. 2039-2040 51. 2040-2041 52. 2041-2042 53. 2042-2043 54. 2043-2044 55. 2044-2045 56. 2045-2046 57. 2046-2047 58. 2047-2048 59. 2048-2049 60. 2049-2050 61. 2050-2051 62. 2051-2052 63. 2052-2053 64. 2053-2054 65. 2054-2055 66. 2055-2056 67. 2056-2057 68. 2057-2058 69. 2058-2059 70. 2059-2060 71. 2060-2061 72. 2061-2062 73. 2062-2063 74. 2063-2064 75. 2064-2065 76. 2065-2066 77. 2066-2067 78. 2067-2068 79. 2068-2069 80. 2069-2070 81. 2070-2071 82. 2071-2072 83. 2072-2073 84. 2073-2074 85. 2074-2075 86. 2075-2076 87. 2076-2077 88. 2077-2078 89. 2078-2079 90. 2079-2080 91. 2080-2081 92. 2081-2082 93. 2082-2083 94. 2083-2084 95. 2084-2085 96. 2085-2086 97. 2086-2087 98. 2087-2088 99. 2088-2089 100. 2089-2090 101. 2090-2091 102. 2091-2092 103. 2092-2093 104. 2093-2094 105. 2094-2095 106. 2095-2096 107. 2096-2097 108. 2097-2098 109. 2098-2099 110. 2099-2100 111. 2100-2101 112. 2101-2102 113. 2102-2103 114. 2103-2104 115. 2104-2105 116. 2105-2106 117. 2106-2107 118. 2107-2108 119. 2108-2109 120. 2109-2110 121. 2110-2111 122. 2111-2112 123. 2112-2113 124. 2113-2114 125. 2114-2115 126. 2115-2116 127. 2116-2117 128. 2117-2118 129. 2118-2119 130. 2119-2120 131. 2120-2121 132. 2121-2122 133. 2122-2123 134. 2123-2124 135. 2124-2125 136. 2125-2126 137. 2126-2127 138. 2127-2128 139. 2128-2129 140. 2129-2130 141. 2130-2131 142. 2131-2132 143. 2132-2133 144. 2133-2134 145. 2134-2135 146. 2135-2136 147. 2136-2137 148. 2137-2138 149. 2138-2139 150. 2139-2140 151. 2140-2141 152. 2141-2142 153. 2142-2143 154. 2143-2144 155. 2144-2145 156. 2145-2146 157. 2146-2147 158. 2147-2148 159. 2148-2149 160. 2149-2150 161. 2150-2151 162. 2151-2152 163. 2152-2153 164. 2153-2154 165. 2154-2155 166. 2155-2156 167. 2156-2157 168. 2157-2158 169. 2158-2159 170. 2159-2160 171. 2160-2161 172. 2161-2162 173. 2162-2163 174. 2163-2164 175. 2164-2165 176. 2165-2166 177. 2166-2167 178. 2167-2168 179. 2168-2169 180. 2169-2170 181. 2170-2171 182. 2171-2172 183. 2172-2173 184. 2173-2174 185. 2174-2175 186. 2175-2176 187. 2176-2177 188. 2177-2178 189. 2178-2179 190. 2179-2180 191. 2180-2181 192. 2181-2182 193. 2182-2183 194. 2183-2184 195. 2184-2185 196. 2185-2186 197. 2186-2187 198. 2187-2188 199. 2188-2189 200. 2189-2190 201. 2190-2191 202. 2191-2192 203. 2192-2193 204. 2193-2194 205. 2194-2195 206. 2195-2196 207. 2196-2197 208. 2197-2198 209. 2198-2199 210. 2199-2200 211. 2200-2201 212. 2201-2202 213. 2202-2203 214. 2203-2204 215. 2204-2205 216. 2205-2206 217. 2206-2207 218. 2207-2208 219. 2208-2209 220. 2209-2210 221.	
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Reuben Johnson
(Signature)

Please delete the title “ASYMMETRIC SYNTHESIS PROCESS” and replace with -- ASYMMETRIC SYNTHESIS PROCESS --.

In the claims

On the line preceding the claims, insert -- What is claimed is: --

Please cancel claims 1-9 without prejudice.

Claim 10, line 1, change "The compounds" to -- A compound --.

Claim 12, line 1, before "compound" change "The" to -- A --.

Claim 14, line 1, before "compound" change "The" to -- A --.

Claim 15, line 1, before "compound" change "The" to -- A --.

Claim 17, line 1, before "compound" change "The" to -- A --.

Claim 19, line 1, before "compound" change "The" to -- A --.

Claim 21, line 1, before "compound" change "The" to -- A --.

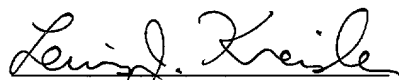
Claim 23, line 1, before "compound" change "The" to -- A --.

Claim 25, line 1, before "compound" change "The" to -- A --.

REMARKS

By this Amendment all claims, other than claims 10-27, have been canceled. Therefore claims 10-27 are pending. The independent claims have been amended to begin with the indefinite article. Entry of this Amendment is respectfully requested.

Respectfully submitted,



Attorney of Applicant(s)

Lewis J. Kreisler

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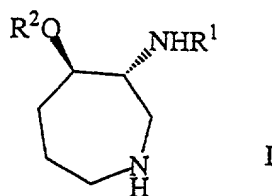
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The present invention is concerned with a novel process for the manufacture of azepines and with intermediates used in this process.

The present invention is concerned with a process for the
15 manufacture of azepines of the formula



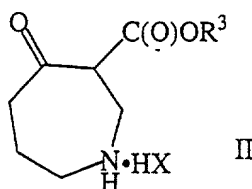
The compounds of formula I include known, pharmacologically active compounds, for example, balanol (see Int. Patent Application WO 93/03730) and other phosphokinase inhibitors, for example, the compounds described in European Patent Application A-0 663 393. The process in accordance with the invention enables such compounds to be manufactured in a simpler and more economical manner than has been possible with previously known processes.

30 In the scope of the present invention, acyl residues R¹ and R² are selected from the group consisting of benzoic acid; benzoic acid

substituted by the group selected from hydroxy, halogen, preferably fluorine, lower-alkyl and lower-alkoxy; benzoyl; and benzoyl substituted by the group selected from fluorine, lower-alkyl and lower-alkoxy. The term "lower" denotes groups with 1-6 C atoms.

- 5 Compounds of formula I in which R^2 is p-hydroxybenzoyl or p-(2-fluoro-6-hydroxy-3-methoxybenzoyl)benzoyl and R^1 is p-hydroxybenzoyl or 4-hydroxy-3,5-dimethylbenzoyl are preferred. R^4 is an amino protecting group, preferably tert.-butoxycarbonyl.

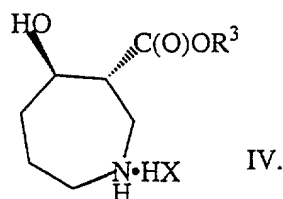
- 10 In one embodiment of the present invention, the novel process for the manufacture of compounds of formula I comprises the catalytic asymmetric hydrogenation of a compound of the formula



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wherein R^3 is lower-alkyl and HX is an acid,

to a compound of the formula



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- Examples of acids HX for the acid addition salts of formula II and formula IV are inorganic acids, such as mineral acids, for example HCl, and organic acids, such as sulphonic acids, for example, p-
 25 toluenesulphonic acid and methanesulphonic acid.

The catalyst for the asymmetric hydrogenation is a complex of an optically active, preferably atropisomeric, diphosphine ligand with a metal of Group VIII of the periodic system, especially

ruthenium. Such catalysts are described, for example, in European Patent Publication A-0 643 052.

As catalysts there come into consideration rhodium-
5 diphosphine complexes of the formulae

- | | | | |
|----|------------------------|-------|-----|
| | $(RuL)^{2+}(X^0)_2$ | III-a | |
| | $(RuLX^2)^{2+}(X^0)_2$ | III-b | |
| | $(RuLX^1X^2)+X^3$ | III-c | and |
| 10 | $RuL(X^4)_2$ | III-d | |
- wherein
- X^0 is selected from the group consisting of BF_4^- , ClO_4^- , $B(phenyl)_4^-$, SbF_6^- , PF_6^- , and $Z^1-SO_3^-$;
- X^1 is halide;
- 15 X^2 is benzene, hexamethylbenzene or p-cymene;
- X^3 is selected from the group consisting of halide, ClO_4^- , $B(phenyl)_4^-$, SbF_6^- , PF_6^- , $Z^1-SO_3^-$ and BF_4^- ;
- X^4 is selected from the group consisting of Z^2-COO^- , $Z^3-SO_3^-$, allyl and $CH_3COCH=C(CH_3)O^-$;
- 20 Z^1 is halogenated lower alkyl or halogenated phenyl;
- Z^2 is selected from the group consisting of lower alkyl, phenyl, halogenated lower alkyl and halogenated phenyl;
- Z^3 is lower alkyl or phenyl; and
- 25 L is an optically active, preferably atropiso-meric, diphosphine ligand.

Especially preferred ligands L are

- | | | |
|----|-----------|--|
| 30 | MeOBIPHEP | (6,6'-Dimethoxybiphenyl-2,2'-diyl)bis-(diphenylphosphine); |
| | BIPHEMP | (6,6'-Dimethylbiphenyl-2,2'-diyl)bis-(diphenylphosphine); |
| 35 | BINAP | ((1,1'-Binaphthyl)-2,2'-diyl)bis-(diphenylphosphine); |

These ligands are described in Patent Publications
30 EP 643 052, EP 647 648, EP 582 692, EP 580 336, EP 690 065,
EP 643 065, JP 523 9076.

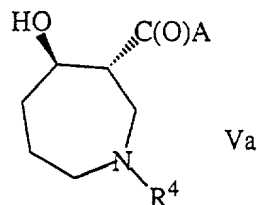
5 The ratio of ruthenium to ligand L in the complexes of formulae III-a to III-d is from about 0.5 mol to about 2 mol, preferably at about 1 mol of ruthenium per mol of ligand. The substrate/catalyst ratio (S/C; mol/mol) is from about 20 to about 30000, preferably from about 100 to about 5000.

The hydrogenation is carried out with the exclusion of oxygen in ethanol under an elevated pressure, for example, at pressures of from about 1 bar to about 100 bar, preferably from about 5 bar to about 70 bar, and at temperatures of from about 0°C to about 80°C, preferably from about 20°C to about 50°C.

The compound of formula IV is converted into a carboxylic acid compound of the formula

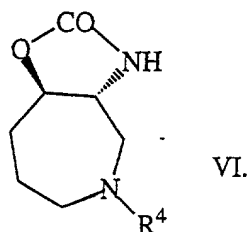


preferably a tert.-butoxycarbonyl group. The ester group R³ of the
25 compound of formula IV is saponified using aqueous alkali, for
example, sodium hydroxide solution, at room temperature. The
carboxylic acid of formula V is then converted by known methods
into an acid azide or acid amide containing compound of the formula



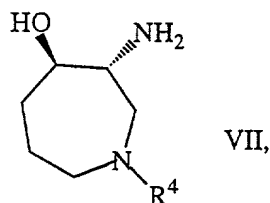
wherein A is azido or amino.

- 5 Subsequent degradation according to Curtius or Hofmann, yields an oxazolidone compound of the formula.



10

The oxazolidone of formula VI is hydrolyzed to a compound having the formula



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in a manner known per se, for example, using aqueous-alcoholic alkali while heating to 70-90°C.

- The hydroxy group and the amino group in the compound of
 20 formula VII are then acylated in a manner known per se, for example, by reaction with a reactive derivative of a carboxylic acid $R^1\text{COOH}$ or $R^2\text{COOH}$, such as a mixed anhydride. When these carboxylic acids contain acylatable groups, such as OH groups, these groups are conveniently intermediately protected. Compounds of formula I in

which R^1 and R^2 are different from one another can be obtained, for example, by N-acylating the amino group in the compound of formula VII selectively with 1 equivalent of $R^1\text{COOH}$ and subsequently O-acylating with 1 equivalent of $R^2\text{COOH}$.

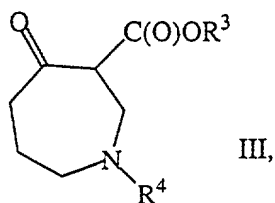
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The protecting group R^4 can be removed in a manner known per se from the compound of formula VII. For example, when R^4 is tert.-butoxycarbonyl group, R^4 can be removed by treatment with an acid, such as 2N HCl in a solvent such as ethyl acetate.

10

Another embodiment of the novel process for the manufacture of compounds of formula I, in accordance with the present invention, comprises

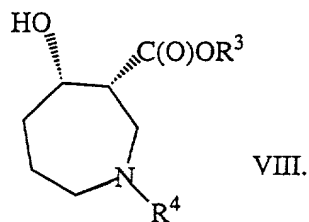
15 microbially reducing a compound of the formula



wherein R^3 is lower alkyl and R^4 is a protecting group,

20

to a compound having the formula



25 In principal, the reduction is not limited to a specific microorganism. Fungus strains (fungi), especially yeasts, are conveniently used as the microorganisms. An especially preferred microorganism is *Hanseniaspora uvarum* R 1052, especially the

strain deposited on 16.1.1996 at the Deutschen Sammlung von Mikroorganismen und Zellkulturen (DSMZ) under No. DSM 10 496.

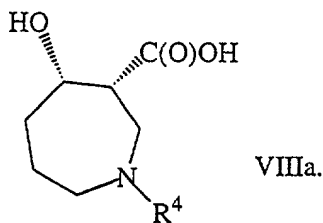
5 The reduction of a compound III to a compound of formula IV
can be carried out using intact cell cultures or using enzymes
obtained from the microorganisms. The preferred microorganism,
Hanseniaspora uvarum R 1052, can be cultivated in aerobic aqueous
submersed cultures on usual nutrient substrates which contain
carbon and nitrogen sources, for example, glucose or starch, and,
10 respectively, soya meal, yeast extract or peptone, as well as
inorganic salts, such as ammonium sulphate, sodium chloride or
sodium nitrate. The cultivation can be carried out at temperatures
of about 20-35°C, preferably at 27°C, in a pH range of about 3-9,
preferably at about pH 5-7.

15

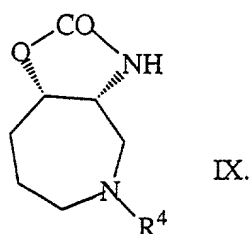
The compound of formula III is added to the culture of the
microorganism in an organic solvent, for example, ethyl acetate.
The course of the reduction can be followed by thin-layer chroma-
tography of samples of the reaction medium. In general, the reaction
20 takes about 8-12 hours. The reaction product, the compound of
formula VIII, can be separated from the culture solution by
extraction with a suitable organic solvent, for example, with ethyl
acetate.

25 In the next reaction step, the compound of formula VIII is
saponified, using aqueous alkali, for example, sodium hydroxide
solution, at room temperature, to its corresponding carboxylic acid.
The carboxylic acid is then converted using known methods into an
acid azide or acid amide containing compound of the formula

30

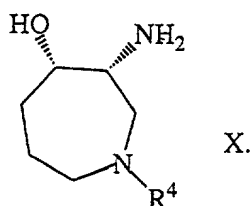


Subsequent degradation according to Curtius or Hofmann yields an oxazolidone compound of the formula



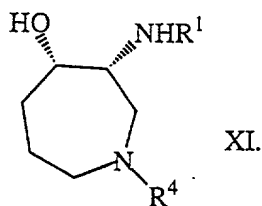
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By alkaline hydrolysis of the oxazolidone IX, for example by using aqueous-alcoholic alkali while heating to 70-90 °C, there is obtained a compound of the formula



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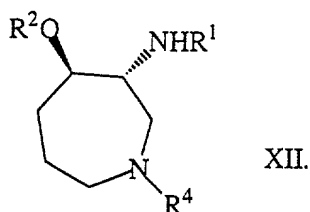
The hydroxy group and the amino group in the compound of formula X are then acylated in a manner known per se, for example, by reaction with a reactive derivative of a carboxylic acid $R^1 COOH$ or $R^2 COOH$, such as a mixed anhydride. The compound of formula X is preferably N-acylated with an aromatic carboxylic acid of the formula $R^1 COOH$ to a compound having the formula



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The compound of formula XI is then acylated with an aromatic carboxylic acid or a reactive derivative thereof, of the formula

R²OH, in the presence of triphenylphosphine and diethyl azo-dicarboxylate, to yield a compound having the formula



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The protecting group R⁴ can be removed in a manner known per se from the compound of formula XII. For example, when R⁴ is tert.-butoxycarbonyl group, R⁴ can be removed by treatment with an acid, such as 2N HCl in a solvent such as ethyl acetate.

The intermediate compounds of the formulae II, IV, V, VI, VIII, VIIIa, IX, X and XI as well as the compound prepared in Example 12a and, respectively, 17 are novel and are likewise objects of the present invention.

The invention is illustrated in more detail by the following Examples, however is in no manner limited thereby. In these Examples, the abbreviations used have the following significance: „ee” is „enantiomeric excess”, which is defined as percent of R-product minus percent of S-product; „dec.” is „decomposition”; HPLC is high performance liquid chromatography.

Example 1

25

Preparation of compounds of formula II and formula III.

a) A solution of 218.3 g of di-tert-butyl dicarbonate in 250 ml of dichloromethane was added at 20-25°C while stirring, in the course of 1 hour, to 101.2 g of piperidin-3-ol in 750 ml of dichloromethane. The reaction mixture was stirred at room temperature for a further 2 hours. Thereafter, a solution of 33.6 g

- of sodium bicarbonate and 11.9 g of potassium bromide in 1000 ml of deionized water was added and the reaction mixture was cooled to -2°C . After the addition of 0.39 g of 2,2,6,6-tetramethyl-piperidine 1-oxide, 560 g of 13.3% aqueous sodium hypochlorite solution were added at $0-5^{\circ}\text{C}$ in the course of 80 minutes. After stirring at -2°C for a further 30 minutes, the excess sodium hypochlorite solution was added at $0-5^{\circ}\text{C}$ in the course of 80 minutes. After stirring at -2°C for a further 30 minutes, the excess sodium hypochlorite was destroyed by the addition of about 10 ml of 38% aqueous sodium bisulphite solution. The reaction mixture was then warmed to 20°C and the aqueous layer was separated and extracted with 500 ml of dichloromethane. Both organic phases were washed with 500 ml of 10% sodium chloride solution, combined and dried over sodium sulphate. After filtration and removal of the solvent under reduced pressure the oily residue was purified by distillation under reduced pressure which yielded 191.2 g of tert-butyl 3-oxo-piperidine-1-carboxylate as a colourless oil, boiling point $80-82^{\circ}\text{C}/0.01\text{ mbar}$.
- b) 99.6 g of the compound obtained in paragraph a) were dissolved in 600 ml of diethyl ether. The solution was cooled to -70°C and the white suspension was treated simultaneously and dropwise in the course of 1 hour with solutions of 62.0 ml of ethyl diazoacetate in 125 ml of diethyl ether and 69.0 ml of boron trifluoride etherate in 125 ml of diethyl ether, with the internal temperature being held at -70°C . After stirring at -70°C for a further 1 hour the cooling bath was removed, the reaction mixture was warmed to 0°C and treated with 375 ml of 10% sodium carbonate solution. The aqueous phase was separated and extracted with 250 ml of diethyl ether. The organic phases were washed with 250 ml of 10% sodium chloride solution, combined and dried over sodium sulphate. The solvent was removed under reduced pressure at 30°C yielding ethyl 1-(tert-butoxycarbonyl)-4-oxo-azepan-3-carboxylate as a crude product in the form of a yellow oil, which was used in the next step without further purification.

- c) 147.2 g of the product obtained in paragraph b) were dissolved in 1250 ml of dioxan and seeded with 0.1 g of ethyl 4-oxo-azepan-3-carboxylate hydrobromide. Thereafter, 175 ml of 5.7M HBr/ethyl acetate were added at room temperature, while stirring, in the
- 5 course of 25 minutes. After further seeding with 0.1 g of ethyl 4-oxo-azepan-3-carboxylate hydrobromide, the suspension was stirred at room temperature for 5 hours. The crystals were filtered off, washed with ethyl acetate and dried at 50°C and 25 mbar. The resulting 91.0 g of crude ethyl 4-oxo-azepan-3-carboxylate
- 10 hydrobromide was dissolved in 1250 ml of 2-butanone while stirring and heating under reflux. The solution was cooled to 65°C and seeded with 0.1 g of pure ethyl 4-oxo-azepan-3-carboxylate hydrochloride. After cooling to room temperature, the suspension was stirred at room temperature for 1 hour and at 0°C for 3 hours.
- 15 The crystals were filtered off, washed with 200 ml of 2-butanone (cooled to -10°C) and dried at 50°C and 25 mbar, yielding 68.2 g of white ethyl 4-oxo-azepan-3-carboxylate hydrobromide, melting point 127-130°C (dec.).
- 20 d) 59.4 g of the compound obtained in paragraph b) were dissolved in 1000 ml of 1M HCl in dioxan and stirred at room temperature for 24 hours. After a reaction period of 1.5 hours the solution was seeded with about 25 mg of ethyl 4-oxo-azepan-3-carboxylate hydrochloride. The white suspension was filtered,
- 25 washed with dioxan and dried at 50°C and 25 mbar, yielding 31.3 g of ethyl 4-oxo-azepan-3-carboxylate hydrochloride in the form of white crystals, which contained about 0.4 mol of dioxan per mol of hydrochloride according to the NMR spectrum. The hydrochloride was recrystallized for further purification and in order to remove the
- 30 dioxan. 31.3 g of ethyl 4-oxo-azepan-3-carboxylate hydrochloride were dissolved in 600 ml of 2-butanol at 80°C and the solution was cooled to -20°C in the course of 2 hours and stirred at -20°C for 3 hours. The white suspension was filtered, washed with 2-butanol (cooled to -20°C) and dried at 50°C and 25 mbar to yield 22.9 g of
- 35 ethyl 4-oxo-azepan-3-carboxylate hydrochloride in the form of white crystals, melting point 145-148°C (dec.).

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Example 2

75.0 g of ethyl 4-oxo-azepan-3-carboxylate hydrochloride and
5 800 ml of ethanol were introduced into an autoclave. The autoclave
was closed and the air was removed therefrom by repeated
evacuation to about 0.1 bar and pressurization with argon (7 bar)
and hydrogen (40 bar) while stirring. Thereafter, a solution of
226 mg of diacetoxy-ruthenium (R)-6,6'-dimethoxybiphenyl-2,2-
10 diyl)-bis(diphenylphosphine) in 20 ml of ethanol was fed into the
autoclave at 2 bar hydrogen pressure with the exclusion of oxygen.
Thereafter, hydrogen pressure was increased to 40 bar and the
reaction mixture was hydrogenated while stirring at 30°C for
19 hours and at 50°C for 3 hours. Thereafter, the content of the
15 autoclave was washed out with 200 ml of ethanol and the combined
solutions were evaporated at 50°C/ 100 mbar and the brown residue
was dried for 2 hours. The residue (75.9 g, consisting of about 80%
3R,4R and 20% 3S,4R isomers) was triturated with 450 ml of
tetrahydrofuran at 24°C for 19 hours and at 16°C for 1 hour. The
20 crystals were filtered off under suction, washed with
tetrahydrofuran and dried to constant weight at 50°C/20 mbar for
3.5 hours. There were obtained 56.3 g of light beige crystals,
which were again triturated with 225 ml of tetrahydrofuran as
previously described. The crystals were removed by suction
25 filtration and dried, yielding 55.1 g of ethyl (3R,4R)-4-hydroxy-
azepan-3-carboxylate hydrobromide in the form of white crystals,
which were enantiomerically pure according to HPLC.

Example 3

30

As in Example 2, 23.2 g of ethyl 4-oxo-azepan-3-carboxylate
hydrochloride in 90 ml of ethanol were hydrogenated with a solution
of 36.1 mg of the ruthenium catalyst in 10 ml of ethanol under
40 bar hydrogen pressure at 30°C for 21 hours and at 50°C for
35 3 hours. The residue, consisting of about 80% 3R,4R and 20% 3S,4R
isomers, was triturated with tetrahydrofuran and ethanol at 50°C

- for half an hour and at room temperature for 4 hours. The crystals were filtered off under suction, washed with a small amount of tetrahydrofuran/ethanol and dried to constant weight at 50°C/20 mbar, to yield 13.3 g of enantiomerically pure ethyl (3R,4R)-4-hydroxy-azepan-3-carboxylate hydrochloride in the form of white crystals.

Example 4

- 10 As in Example 2, 0.44 g of ethyl 4-oxo-azepan-3-carboxylate hydrochloride in 9 ml of ethanol was hydrogenated with a solution of 3.2 mg of $\text{di}(\eta^2\text{-acetato})(\eta^4\text{-cycloocta-1,5-diene})\text{-ruthenium(II)}$ and 5.8 mg (R)-MeOBIPHEP in 1 ml of diethyl ether/THF 3/1 under 40 bar hydrogen pressure at 25°C for 23.5 hours. The yellow
- 15 hydrogenation solution was evaporated on a rotary evaporator at 40°/20 mbar. With a conversion of 83%, the residue consisted, according to HPLC analysis, of 65% ethyl (3R,4R)-4-hydroxy-azepan-3-carboxylate hydrochloride with an ee >99%.

20

Example 5

The hydrogenations set forth in Table 1 were carried out in an analogous manner to Examples 2-4.

Table 1

Asymmetric hydrogenation of ethyl 4-oxo-azepan-3-carboxylate.HX¹⁾

5

Ex No	L	X	Solv.	T °C	Press. bar	Conv./ hr	trans ³⁾		cis	
							%	ee	%	ee
5a	(S)-BINAP	Cl	2)	25	40	62/23	78	>99	22	73
5b	(R)-BIPHEMP	Cl	2)	25	40	90/23	66	94	34	38
5c	(R)-pTol- BIPHEMP	Cl	2)	25	40	93/23	72	>99	28	62
5d	(R)-p-An- MeOBIPHEP	Cl	2)	25	40	87/23	80	>99	20	77
5e	(R)-mTol- BIPHEMP	Cl	2)	25	40	90/24	58	97	42	47
5f	(R)-pDMA- MeOBIPHEP	Cl	2)	25	40	79/24	72	>99	28	95
5g	(R)-pPhenyl- MeOBIPHEP	Cl	2)	25	40	54/23	82	>99	18	26
5h	(S)-3,5-Me,4- MeO-MeOBIPHEP	Cl	2)	25	40	34/23	55	>99	45	61
5i	(R)-DiMeOBIPHEP	Cl	2)	25	40	99/23	66	>99	34	86
5j	(R)-MeOBIPHEP	Br	EtOH	40	100	99/21	76	>99	24	84
5k	"	Br	EtOH	60	100	100/21	69	>99	31	85
5l	(R)-2-Furyl- MeOBIPHEP	Br	EtOH	40	100	76/29	64	98	36	95
5m	(R)-2-Furyl-2- Biphemp	Br	EtOH	40	100	94/21	68	>99	32	69
5n	(R)-TriMeOBIPHEP	Br	EtOH	30	100	100/23	76	>99	24	95
5o	(R)-Cy2- MeOBIPHEP	Cl	EtOH	80	20	100/22	38	>99	62	92
5p	(R)-MeOBIPHEP	Cl	MeOH	30	100	100/22	75	>99	25	88
5q	"	Cl	iPrOH	"	"	90/22	78	>99	22	84
5r	"	Cl	AcOH	25	40	97/23	5	>99	95	94

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- 1) Catalyst preparation analogously to Example 2 and 3.
- 2) Catalyst preparation: in situ analogously to Example 4,
solvent: ethanol-diethyl ether-tetrahydrofuran 9:0.65:0.35.
- 3) trans: compound IV or its enantiomer. Chiral diphosphine
ligands with (R)-configuration give (3R,4R)-IV.

Example 6

As in Example 3, 3.32 g of ethyl 4-oxo-azepan-3-carboxylate hydrochloride were hydrogenated in the presence of 6.3 mg of $[\text{RuCl}((\text{R})\text{-MeOBIPHEP})(\text{C}_6\text{H}_6)]\text{Cl}$ under 40 bar hydrogen pressure at 30°C for 19 hours and at 50° for 3 hours. The yellow hydrogenation solution was evaporated on a rotary evaporator at 40°/20 mbar. With a conversion of 95% the residue consisted, according to HPLC analysis, of 79% ethyl (3R,4R)-4-hydroxy-azepan-3-carboxylate with an ee >99%.

Example 7

A catalyst solution was prepared in a glove box (O_2 content < 1 ppm) by dissolving 1.3 ml of a 0.03 molar ethanolic HBr solution and 16.1 mg of $\text{Ru}(\text{OAc})_2((\text{R})\text{-MeOBIPHEP})$ in 10 ml of ethanol and stirring for 0.5 hour. Then, 0.53 g of ethyl 4-oxo-azepan-3-carboxylate hydrobromide and 2 ml of the catalyst solution prepared above were placed in 4 ml of ethanol in an autoclave and hydrogenated at 20°C under 100 bar hydrogen pressure for 21 hours. The yellow hydrogenation solution was evaporated on a rotary evaporator at 40°/20 mbar. With a conversion of 76%, the residue consisted, according to HPLC analysis, of 58% ethyl (3R,4R)-4-hydroxy-azepan-3-carboxylate hydrobromide with an ee >99%.

Example 8

- 5 A catalyst solution was prepared in a glove box (O_2 content < 1 ppm) by dissolving 1.0 ml of a 0.04 molar ethanolic HBf_4 solution and 32.1 mg of $Ru(OAc)_2((R)\text{-MeOBIPHEP})$ in 10 ml of ethanol and stirring for 0.5 hour. Then, 0.53 g of ethyl 4-oxo-azepan-3-carboxylate hydrobromide and 1 ml of the catalyst solution prepared above were placed in 9 ml of ethanol in an autoclave and hydrogenated at $20^\circ C$ under 100 bar hydrogen pressure for 21 hours.
- 10 The yellow hydrogenation solution was evaporated on a rotary evaporator at $40^\circ/20$ mbar. With a conversion of 44% the residue consisted according to HPLC analysis of 37% ethyl (3R,4R)-4-hydroxy-azepan-3-carboxylate hydrobromide with an ee >99%.

Example 9

- 67.0 g of ethyl (3R,4)-4-hydroxy-azepan-3-carboxylate hydrobromide were suspended in 500 ml of tert-butyl methyl ether and treated with 30.4 g of triethylamine. Thereafter, a solution of
- 20 54.6 g of di-tert-butyl dicarbonate in 25 ml of tert-butyl methyl ether was added at room temperature in the course of 20 minutes. Thereafter, the mixture was stirred at room temperature for a further 2 hours.
- 25 500 ml of 2N NaOH were added to the white suspension and the reaction mixture was stirred vigorously at room temperature for 2 hours. The reaction mixture was then acidified with 175 ml of 6N HCl and, after phase separation, the aqueous phase was extracted twice with 100 ml of tert-butyl methyl ether. All organic phases
- 30 were washed with 150 ml of 10% sodium chloride solution, combined and dried over sodium sulphate. After removal of the solvent under reduced pressure at $40^\circ C$ the crude hydroxyacid was dissolved in 260 ml of butyl acetate at about $85^\circ C$. After seeding with pure product the suspension was cooled to $-20^\circ C$ in the course
- 35 of 2 hours and stirred at this temperature overnight. The suspension was filtered, washed with 100 ml of hexane and dried at

50°C and 25 mbar, yielding 55.9 g of (3R,4R)-4-hydroxy-azepan-1,3-dicarboxylic acid 1-tert-butyl ester, melting point 121.5-122.5°C.

5

Example 10

300 ml of ethyl acetate and 20.9 ml of triethylamine were added to 38.9 g of the compound prepared in Example 9. The solution was heated to reflux, then 32.4 ml of diphenylphosphoryl azide were added in the course of 30 minutes and the heating under reflux was continued for a further 2 hours. After cooling to room temperature the reaction mixture was treated with 300 ml of ethyl acetate and washed with 150 ml of 5% sodium hydrogen carbonate solution and twice with 150 ml of water. The aqueous phases were extracted twice with 300 ml of ethyl acetate. The combined organic phases were dried over sodium sulphate and evaporated at 45°C under reduced pressure. The crude crystalline residue was dissolved in 300 ml of butyl acetate, seeded with pure product, cooled to -20°C in the course of about 3 hours and stirred overnight. The suspension was filtered, washed with butyl acetate (pre-cooled to -20°C) and dried at 60°C and 25 mbar to yield 29.9 g of (3aR,8aR)-5-tert-butoxycarbonyl-2-oxo-octahydro-oxazolo[4,b-c]azepine, melting point 152.5-153.5°C.

25

Example 11

25.6 g of the compound prepared in Example 10 were added to 250 ml of methanol and 250 ml of 2N NaOH. The reaction mixture was heated to reflux and held at this temperature for 3 hours. After cooling, 265 ml of solvent were distilled off at 50°C and 150 mbar and the residue was extracted three times with 200 ml of ethyl acetate each time. The three organic phases were washed with 50 ml of 10% sodium chloride solution, combined and dried over sodium sulphate. After removal of the solvent the viscous oil obtained as the residue was dissolved in 100 ml of cyclohexane at 60°C, seeded with pure product, cooled to room temperature in the

course of 2 hours and stirred overnight. The suspension was filtered, washed with 40 ml of cyclohexane and dried at 50°C and 25 mbar, yielding 21.5 g of tert-butyl (3R,4R)-3-amino-4-hydroxy-azepan-1-carboxylate, melting point 99-100.5°C.

5

Example 12

a) 4.58 g of p-toluenesulphonyl chloride dissolved in 24 ml of dichloromethane were added at room temperature in the course of 10 minutes to 4.66 g of 4-tert-butoxybenzoic acid and 6.11 g of 4-dimethylaminopyridine in 30 ml of dichloromethane. After stirring at room temperature for 2 hours, 2.30 g of the compound prepared in Example 6 in 6 ml of dichloromethane were added in the course of 10 minutes. Thereafter, the mixture was stirred at room 15 temperature for 16 hours. The reaction mixture was washed twice with 20 ml of 1N NaOH each time and then with 40 ml of 1N HCl and 40 ml of water. All aqueous phases were extracted with 20 ml of dichloromethane. The combined organic phases were dried over sodium sulphate and the solvent was removed under reduced 20 pressure. The residual white foam was chromatographed over 300 g of silica gel with 6.5 l of hexane-ethyl acetate (2:1). Fractions of 250 ml were collected. Fractions 8-25 were combined and the solvent was evaporated under reduced pressure, there being obtained 5.91 g of a white foam which was dissolved in 80 ml of heptane at 25 60°C. After stirring at -20°C overnight the crystals were filtered off, washed with cold heptane and dried at 50°C and 25 mbar to yield 5.34 g of tert-butyl (3R,4R)-3-(4-tert-butoxy-benzoylamino)-4-(4-tert-butoxy-benzoyloxy)-azepan-1-carboxylate, melting point 125.5-127.5°C.

30

b) 20.0 ml of 5M HCl in ethyl acetate were added at room temperature and while stirring to 5.83 g of the compound obtained in paragraph a) dissolved in 30 ml of ethyl acetate. The reaction mixture was stirred at room temperature overnight and the white 35 precipitate was filtered off and washed three times with 5 ml of ethyl acetate each time and dried at 50°C/25 mbar for 16 hours.

The white powder obtained was dissolved in 50 ml of water and stirred at 50°C for 1 hour. The solution was then lyophilized and yielded 3.97 g of pure 3-(4-hydroxy-benzoylamino)-4-(4-hydroxy-benzoyloxy)-hexahydroazepine hydrochloride.

5

Example 13

Hanseniaspora uvarum R 1052 was cultivated for 3 days at 27°C in a Petri dish containing a solid nutrient substrate. After
10 3 days, 100 ml of liquid nutrient medium in a 500 ml shaking flask was seeded with a loop of this culture. This pre-culture was shaken at 27°C for 18 hours. The cells grew to a density of 5×10^8 cells/ml (stationary phase). The entire pre-culture was used to inoculate a reactor which contained 7500 ml of nutrient medium
15 (containing 1% yeast extract Difco: Bacto Yeast Extract # 0127-17-9, 1% Pepton Difco: Bacto Peptone # 0118-17-0 and 2% glucose in deionized water). After 18 hours, 750 ml of 50% glucose solution and immediately thereafter 29 g of the compound prepared in Example 1b dissolved in 20 ml of ethyl acetate were added in the
20 course of 25 minutes. After 12 hours the culture solution was extracted twice with 2000 ml of ethyl acetate each time. The combined organic phases were dried over sodium sulphate. The solvent was removed under reduced pressure at 30°C to yield 30.1 g of ethyl (3R,4S)-1-(tert-butoxycarbonyl)-4-hydroxy-azepan-3-
25 carboxylate as a viscous orange oil.

Example 14

a) A mixture of 28.7 g of the compound prepared in Example 13 in
30 200 ml of tert-butyl methyl ether and 200 ml of 2N NaOH was stirred vigorously at room temperature for 4 hours and then at 50°C for 20 hours. After cooling, the aqueous phase was extracted twice with 100 ml of tert-butyl methyl ether each time. The organic phases were discarded. The aqueous phase was acidified cautiously
35 with about 70 ml of 6N HCl and extracted once with 200 ml of tert-butyl methyl ether and twice with 100 ml of tert-butyl methyl

ether each time. All three organic phases were washed once with 50 ml of 10% sodium chloride solution, combined and dried over sodium sulphate. After removal of the solvent under reduced pressure (40°C/25 mbar) the brown viscous oil was dissolved in 5 60 ml of isopropyl ether at 60°C and left to crystallize at -20°C for 16 hours. The crystals were filtered off, washed with a small amount of isopropyl ether, cooled to -20°C and dried at 40°C for 5 hours and 25 mbar, yielding 12.0 g of (3R,4S)-4-hydroxy-azepan-1,3-dicarboxylic acid 1-tert-butyl ester of melting point 98.5-10 101.5°C.

b) 140 ml of ethyl acetate, 9.8 ml of triethylamine and 15.9 ml of diphenylphosphoryl azide were added to 18.1 g of the compound obtained in paragraph a). The solution was heated to reflux for 15 2 hours, cooled, diluted with 140 ml of ethyl acetate and washed with 70 ml of 5% sodium hydrogen carbonate solution and twice with 70 ml of water each time. The three aqueous phases were separated and washed three times with 140 ml of ethyl acetate. The combined organic phases were dried over sodium sulphate and 20 the solvent was removed at 45°C/25 mbar. The crude crystalline residue was dissolved in 140 ml of butyl acetate at about 80°C, seeded with pure product, cooled and stirred at -20°C for 6 hours. The suspension was filtered, washed with butyl acetate (cooled to -20°C) and dried at 60°C and 25 mbar overnight, to yield 13.3 g of 25 tert-butyl (3aR,8aS)-2-oxo-octahydro-oxazolo[4,b-c]azepine-5-carboxylate of melting point 158-159°C.

Example 15

30 200 ml of methanol and 200 ml of 2N NaOH were added to 20.5 g of the compound prepared in Example 14b). The reaction mixture was heated to reflux and left at this temperature for 4 hours. After cooling, 200 ml of methanol were distilled off at 50°C and 150 mbar and the residue was extracted three times with 35 160 ml of ethyl acetate each time. The organic phases were washed with 40 ml of 10% sodium chloride solution, combined and dried

over sodium sulphate. After removal of the solvent, the viscous oil obtained as the residue was dissolved in 80 ml of methylcyclohexane at 50°C, seeded with pure product, cooled and stirred at 0°C for 4 hours. The crystals were filtered off, washed with 20 ml of methylcyclohexane and dried at 50°C and 25 mbar overnight, yielding 17.4 g of tert-butyl (3R,4S)-3-amino-4-hydroxy-azepan-1-carboxylate, melting point 64-67°C.

Example 16

10

9.06 g of p-toluenesulphonyl chloride in 75 ml of dichloromethane were added at room temperature to 11.5 g of 4-(tert-butoxy)-benzoic acid and 13.1 g of 4-dimethylaminopyridine in 100 ml of dichloromethane. The reaction mixture was stirred for a further 2 hours. The solution was then added in the course of 1 hour to 11.5 g of the compound prepared in Example 10 dissolved in 50 ml of dichloromethane. After stirring at room temperature for 1 hour, the reaction mixture was washed with 100 ml of 1N NaOH, 100 ml of 1N HCl and 100 ml of water. All aqueous phases were extracted with 50 ml of dichloromethane. The combined organic phases were dried over sodium sulphate and the solvent was separated under reduced pressure. The foam-like residue was dissolved in 400 ml of hot heptane and left to crystallize at room temperature overnight. The crystals were washed with 25 ml of heptane and dried at 50°/25 mbar to yield 17.3 g of tert-butyl (3R,4S)-3-(4-tert-butoxy-benzoylamino)-4-hydroxy-azepan-1-carboxylate of melting point 131.5-132.5°C.

Example 17

30

262 mg of diethyl azadicarboxylate in 2 ml of tetrahydrofuran were added while stirring to 407 mg of the compound prepared in Example 16, 253 mg of 4-(tert-butoxy)-benzoic acid and 394 g of triphenylphosphine in 8 ml of tetrahydrofuran. After stirring at 50°C for 4 hours, the solvent was removed under reduced pressure and the residue was taken up in 20 ml of cyclohexane and washed

once with 20 ml of water and twice with 10 ml of 70% methanol/water each time. The aqueous-alcoholic phase was extracted twice with 10 ml of cyclohexane each time. The combined cyclohexane phases were dried over sodium sulphate and the solvent was removed under reduced pressure. The residual viscous oil was dissolved in 10 ml of hot heptane, seeded with pure end product and left to crystallize at room temperature for 18 hours and yielded 241 mg of tert-butyl (3R,4R)-3-(4-tert-butoxy-benzoylamino)-4-(4-tert-butoxy-benzoyloxy)-azepan-1-carboxylate of melting point 126-128°C. This compound can be reacted further as in Example 12b.

Example 18

12.91 g of p-toluenesulphonyl chloride dissolved in 15 ml of dichloromethane were added at room temperature in the course of 15 minutes to 1.94 g of 4-(tert-butoxy)-benzoic acid and 2.63 g of 4-dimethylaminopyridine in 20 ml of dichloromethane. The reaction mixture was stirred for 2 hours and added in the course of 1 hour to 2.30 g of tert-butyl (3R,4R)-3-amino-4-hydroxy-azepan-1-carboxylate dissolved in 10 ml of dichloromethane. After stirring for 1 hour the reaction mixture was washed with 20 ml of 1N NaOH, 20 ml of 1N HCl and 20 ml of water. All aqueous phases were washed in succession with 10 ml of dichloromethane. The combined organic phases were dried over sodium sulphate, filtered and the solvent was evaporated. The foam-like residue obtained was dissolved in 80 ml of hot heptane and crystallized at room temperature overnight. The crystals were washed with 10 ml of heptane and dried to yield 3.23 g of tert-butyl (3R,4R)-3-(4-tert-butoxy-benzoylamino)-4-hydroxy-azepan-1-carboxylate, m.p. 134-135°C.

Example 19

572 mg of p-toluenesulphonyl chloride in 3.5 ml of dichloromethane were added at room temperature in the course of

10 minutes to 679 mg of 4-benzoyl-benzoic acid and 764 mg of 4-dimethylaminopyridine in 5 ml of dichloromethane. After further stirring at room temperature for 2 hours 1016 mg of tert-butyl (3R,4R)-3-(4-tert-butoxy-benzoylamino)-4-hydroxy-azepan-1-carboxylate in 2.5 ml of dichloromethane were added in the course of 10 minutes while stirring. Thereafter, the reaction mixture was stirred at room temperature for a further 2.5 hours and washed with 6 ml of 1N NaOH, 6 ml of 1N HCl and 6 ml of water. All aqueous phases were extracted in succession with 6 ml of dichloromethane. The combined organic phases were dried over sodium sulphate and the solvent was evaporated. The crude product was chromatographed over 100 g of silica gel with 1.4 l of hexane/ethyl acetate (2:1). Fractions of 100 ml were collected. Fractions 5-9 were combined and the solvent was evaporated. There were obtained 1.48 g of a white foam, which was crystallized from 50 ml of hot heptane, to yield 1.24 g of tert-butyl (3R,4R)-3-(4-tert-butoxy-benzoylamino)-4-(4-benzoyl-benzoyloxy)-azepan-1-carboxylate, m.p. 145-148°C, as a white powder.

20

Example 20

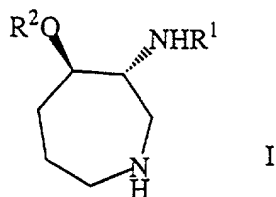
3.0 ml of 5N HCl in ethyl acetate were added at room temperature while stirring to 922 mg of the azepine prepared in Example 19 in 4.0 ml of ethyl acetate. The reaction mixture was stirred at room temperature overnight and the precipitate was filtered off, washed three times with 2 ml of ethyl acetate and dried at 50°C/25 mbar for 16 hours yielding 0.70 g of 3-(4-hydroxy-benzoylamino)-4-(4-benzoyl-benzoyloxy)-hexahydroazepine hydrochloride.

30

Claims

1. A process for the manufacture of compounds of the formula

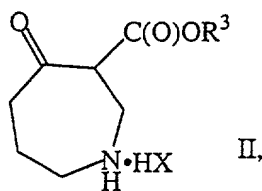
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wherein R¹ and R² are independently an acyl residue of an aromatic carboxylic acid,

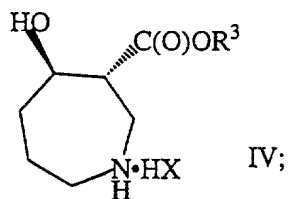
10 comprising:

- a) asymmetrically hydrogenating a compound of the formula



15

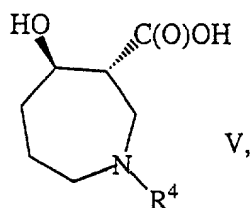
wherein R³ is lower-alkyl,
to a compound of the formula



20

- b) providing a protecting group to the compound of formula IV;

c) saponifying the compound of formula IV after step b), forming a compound of the formula

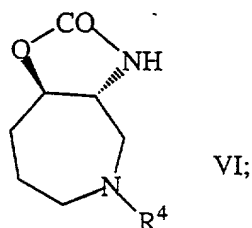


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wherein R^4 is a protecting group;

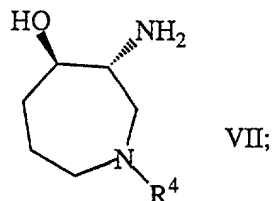
d) converting the compound of formula V into a compound of the formula

10



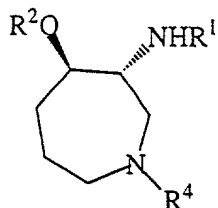
e) hydrolyzing the compound of formula VI into a compound of the formula

15



f) N- and, respectively, O-acylating the compound of formula VII with an aromatic carboxylic acid of the formula R^1COOH or R^2COOH to form a compound of the formula

20



XII; and

g) cleaving off protective groups on the compound of formula XII, to form the compound of formula I.

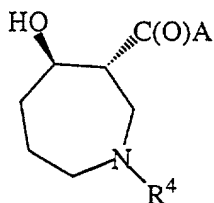
5

2. The process of claim 1, wherein R¹ and R² are p-hydroxybenzoyl.

3. The process of claim 1, further comprising in step c

10

i) converting the compound of formula V into a compound of the formula



Va,

15

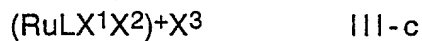
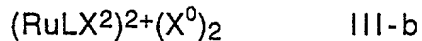
wherein A is azido or amino; and

ii) performing a Curtius or Hofmann degradation on the compound of formula Va to yield the compound of formula VI.

20

4. The process of claim 1, wherein the compound of formula II is hydrogenated in the presence of a rhodium-diphosphine complex catalyst having a formula selected from the formulae

25



and

X^0 is selected from the group consisting of BF_4^- , ClO_4^- , $B(phenyl)_4^-$, SbF_6^- , PF_6^- and $Z^1-SO_3^-$;

X² is benzene, hexamethylbenzene or p-cymene;

5 X² is benzene, hexamethylbenzene or p-cymene;
 X³ is selected from the group consisting of halide, ClO₄⁻,
 B(phenyl)₄⁻, SbF₆⁻, PF₆⁻, Z¹-SO₃⁻ and BF₄⁻;

X⁴ is selected from the group consisting of Z²-COO⁻, Z³-SO₃⁻, allyl and CH₃COCH=C(CH₃)O⁻;

10 Z¹ is halogenated lower alkyl or halogenated phenyl;

Z² is selected from the group consisting of lower alkyl, phenyl, halogenated lower alkyl and halogenated alkyl;

15 Z^3 is lower alkyl or phenyl; and

L is an optically active atropiso-meric, diphosphine ligand.

5. The process of claim 4, wherein L is selected from the group consisting of

20 MeOBIPHEP (6,6'-Dimethoxybiphenyl-2,2'-diyl)bis-(diphenylphosphine);

BIPHEMP (6,6'-Dimethylbiphenyl-2,2'-diyl)bis-(diphenylphosphine);

25 BINAP [(1,1'-Binaphthyl)-2,2'-diyl]bis-(diphenylphosphine);

pTol-BIPHEMP (6,6'-Dimethylbiphenyl-2,2'-diyl)bis(di-(p-tolyl)phosphine);

30 pAn-MeOBIPHEP 6,6'-Dimethoxy-P,P,P',P'-tetrakis-(4-methoxy-phenyl)-biphenyl-2,2'-bis-phosphine;

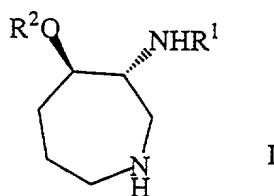
pDMA-MeOBIPHEP 6,6'-Dimethoxy-P,P',P'-tetrakis-(4-dimethylamino-phenyl)-biphenyl-2,2'-bis-phosphine;

pPhenyl-MeOBIPHEP	(6,6'-Dimethoxybiphenyl-2,2'-diyl)-bis(bis-(biphenyl)-phosphine);
mTol-BIPHEMP	(6,6'-Dimethylbiphenyl-2,2'-diyl)bis(di-(m-tolyl)phosphine);
5 Cy ₂ -MeOBIPHEP	P ₂ ,P ₂ -Dicyclohexyl-6,6'-dimethoxy-P ₂ ',P ₂ '-diphenyl-biphenyl-2,2'-bis-phosphine;
2-Furyl ₂ -BIPHEMP	P,P-Diphenyl-P',P'-di-2-furyl-(6,6'-dimethyl-biphenyl-2,2'-diyl)diphosphine;
10 (3,5-Me,4-MeO)-MeOBIPHEP	6,6'-Dimethoxy-P,P,P',P'-tetrakis-(dimethyl-4-methoxy-phenyl)-biphenyl-2,2'-bis-phosphine;
DiMeOBIPHEP	(5,5',6,6'-Tetramethoxybiphenyl-2,2'-diyl)bis(diphenylphosphine);
15 TriMeOBIPHEP	(4,4',5,5',6,6'-Hexamethoxybiphenyl-2,2'-diyl)bis(diphenylphosphine); and
2-Furyl-MeOBIPHEP	(6,6'-Dimethoxybiphenyl-2,2'-diyl)bis-(di-2-furylphosphine).

20

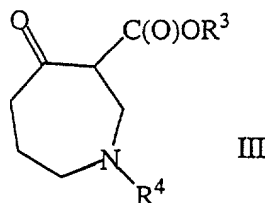
6. The process of claim 5, wherein the catalyst is Ru(OAc)₂(R)-MeOBIPHEP.

25 7. A process for the manufacture of compounds of the formula



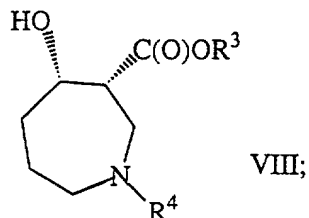
wherein R^1 and R^2 are independently an acyl residue of an aromatic carboxylic acid, comprising:

- 5 a) microbially reducing a compound of the formula

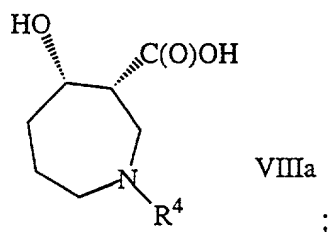


wherein R^3 is lower-alkyl and R^4 is a protecting group,

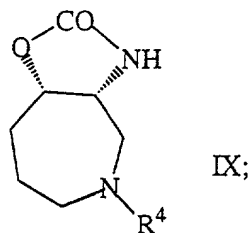
- 10 to a compound of the formula



- 15 b) saponifying the compound of formula VIII to a compound of the formula

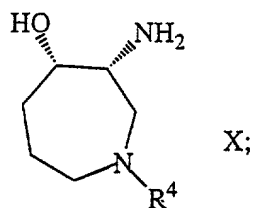


- 20 c) transforming the compound of formula VIIIa into a compound of the formula



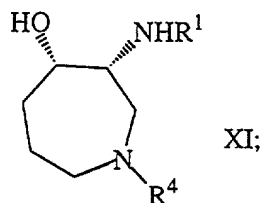
d) hydrolyzing the compound of formula IX into a compound of the formula

5



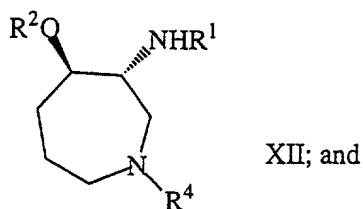
e) acylating the compound of formula X with an aromatic carboxylic acid of the formula R^1COOH to a compound of the formula

10



f) acylating the compound of formula XI with an aromatic carboxylic acid or a reactive derivative thereof, to form a compound of the formula

15



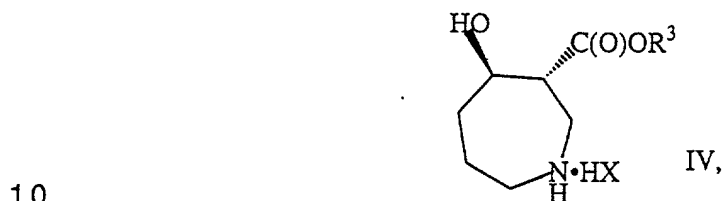
g) cleaving off the protecting group R^4 from the compound of formula XII yielding the compound of formula I.

20

8. The process of claim 7, wherein the compound of formula III is reduced using a culture of *Hanseniaspora uvarum* R 1052.

5 9. The process of claim 7, wherein R^1 and R^2 are p-hydroxybenzoyl.

10. The compounds of the formula



wherein R^3 is lower alkyl.

11. The compound of claim 10, ethyl (3R,4R)-4-hydroxy-
15 azepan-carboxylate hydrochloride.

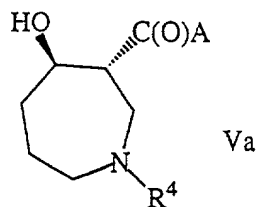
12. The compound of the formula



wherein R^4 is a protecting group.

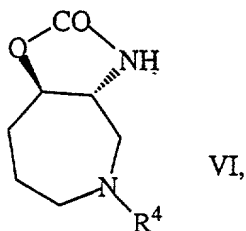
13. The compound of claim 12, (3R,4R)-4-Hydroxy-azepan-
1,3-dicarboxylic acid 1-tert.-butyl ester.
25

14. The compound of the formula



5 wherein A is azido or amino and R⁴ is a protecting group.

15. The compound of the formula



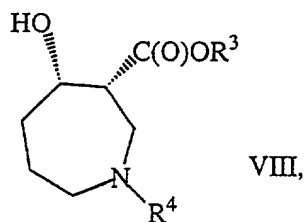
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wherein R⁴ is a protecting group.

16. The compound of claim 15, (3aR,8aR)-5-tert-Butoxycarbonyl-2-oxo-octahydro-oxazolo(4,b-c)azepine.

15

17. The compound of the formula

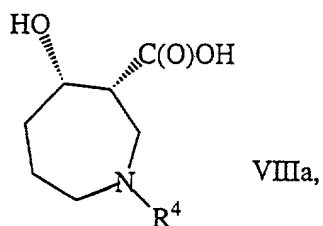


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wherein R³ is lower alkyl and R⁴ is a protecting group.

18. The compound of claim 17, ethyl (3R,4S)-1-(tert-butoxycarbonyl)-4-hydroxy-azepan-3-carboxylate.

19. The compound of the formula



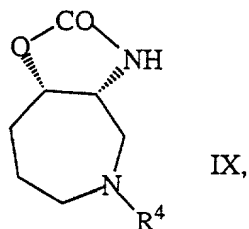
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wherein R^4 is a protecting group.

20. The compound of claim 19, (3R,4S)-4-Hydroxy-azepan-1,3-dicarboxylic acid 1-tert-butyl ester.

10

21. The compound of the formula



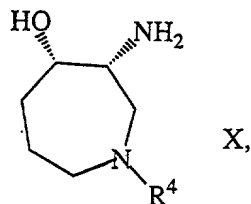
15

wherein R^4 is a protecting group.

22. The compound of claim 21, tert-Butyl (3aR,8aS)-2-oxo-octahydro-oxazolo(4,b-c)azepine-5-carboxylate.

20

23. The compound of the formula



wherein R^4 is a protecting group.

5 25. The compound of the formula



10

27. The compound tert-Butyl (3R,4R)-3-(4-tert-butoxy-
15 benzoylamino)-4-(4-tert-butoxy-benzoyloxy)-azepan-1-carboxylate.

* * *

Declaration and Power of Attorney for Patent Application

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

ASYMMETRIC SYNTHESIS PROCESS

the specification of which

(check one)

☒ is attached hereto

☐ was filed on _____ as

Application Serial No. _____

and was amended on _____

(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, § 1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, § 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)

Priority Claimed

<u>96105998.7</u>	<u>Europe</u>	<u>17 / April / 1996</u>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
<u> </u>	<u> </u>	<u> </u>	<input type="checkbox"/>	<input type="checkbox"/>
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
<u> </u>	<u> </u>	<u> </u>	<input type="checkbox"/>	<input type="checkbox"/>
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No

[illegible]

(Status)
(patented, pending, abandoned)

(Status)
(patented, pending, abandoned)

(Supply similar information and signature for third and subsequent joint inventors.)

Ulrich Zutter

Date _____

March 17, 1997

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Under this section, information is material to patentability when it is not cumulative to information already of record or being made of record in the application, and

- (1) It establishes, by itself or in combination with other information, a *prima facie* case of unpatentability of a claim: or
- (2) It refutes, or is inconsistent with, a position the applicant takes in:
 - (i) Opposing an argument of unpatentability relied on by the Office, or
 - (ii) Asserting an argument of patentability.